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Atty. Docket No.:  
HMSU-P14-006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ingham, et al )  
Serial No.: 09/711724 ) Group Art Unit: 1646  
Filed: 23-Nov-2000 ) Examiner: To Be Assigned  
Title: VERTEBRATE EMBRYONIC )  
PATTERN-INDUCING PROTEINS )  
AND USES RELATED THERETO )

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CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

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INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. 1.97(b)

Submitted herewith on Form PTO-1449 is a list of documents known to Applicants, their Agent and/or Attorney in compliance with the requirements of 37 C.F.R. 1.56. A copy of each document listed is also being submitted herewith.

This Information Disclosure Statement is being filed before the mailing date of the first Office Action on the merits, therefore, no fee is due.

Applicants respectfully request that the Examiner consider the listed documents and indicate that they were considered by making appropriate notations on the attached Form PTO-1449.




This submission does not represent that a search has been made or that no better art exists. Nor does it constitute an admission that each or all of the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claim in the application and applicants determine that the cited documents do not constitute "prior art" under United States law, Applicants reserve the right to present to the Office the relevant facts and law regarding the appropriate status of such documents.

Applicants further reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

If there is any fees due in connection with the filing of this Statement, please charge the fees to our **Deposit Account, No. 18-1945.**

Respectfully submitted,  
Ropes & Gray

By:   
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## INFORMATION DISCLOSURE CITATION

## PRIORITY APPLICATION

(Use several sheets if necessary)

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## U.S. PATENT DOCUMENTS

EXAMINER TRADEMARK OFFICE	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
AA	5,223,408	6/29/93	Goddel et al.	435	69.3	11-Jul-1991
AB	5,585,087	12/17/96	Lustig et al.	424	9.2	08-Jun-1994

## FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	Translation	
						YES	NO
AC	WO 90/02809	3/22/90	PCT	C12P	21/00		
AD	WO 92/15679	9/17/92	PCT	C12N	15/10		

## OTHER DOCUMENTS

(Including Author, Title, Date, Pertinent Pages Etc.)

AE	Anderson, R. et al., "Maintenance of ZPA signaling in cultured mouse limb bud cells", <i>Devel.</i> <u>117</u> :142-1433 (1993).
AF	Angier, N. "Biologists find key genes that shape patterning of embryos", <i>New York Times</i> , Jan 11, 1994, C-1.
AG	Basler, K.I., and G. Struhl, "Compartment boundaries and the control of <i>Drosophila</i> limb pattern by <i>hedgehog</i> protein", <i>Nature</i> <u>368</u> :208-214 (1994).
AH	Basler, K. et al., "Control of Cell Pattern in the Neural Tube: Regulation of Cell Differentiation by <i>dorsalin-1</i> , a Novel TGF $\beta$ Family Member", <i>Cell</i> <u>73</u> : 687-702 (May 21, 1993).
AI	Bass, S. et al., "Hormone phage: An Enrichment Method for Variant Proteins with Altered Binding Properties", <i>PROTEINS: Structure, Function, and Genetics</i> <u>8</u> :309-314 (1990).
AJ	Bejsovec, A. and E. Wieschaus, "Segment polarity gene interactoins modulate epidermal patterning in <i>Drosophila</i> embryos", <i>Devel.</i> <u>119</u> :501-517 (1993).
AK	Bienz, M., "Homeotic genes and positional signalling in the <i>Drosophila</i> viscera", <i>TIG</i> <u>10</u> :22-26 (Jan. 1994).
AL	Bitgood, M. and McMahon, A., "Hedgehod and Bmp Genes are Coexpressed at Many Diverse Sites of Cell-Cell Internation in the Mouse Embryo", <i>Dev. Biol.</i> <u>172</u> (1):126-138 (1995).
AM	Blair, S.S., "Hedgehog digs up an old Friend", <i>Nature</i> <u>373</u> :656-657 (23 Feb. 1995).
AN	Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions", <i>Science</i> <u>247</u> :1306-1310
AO	Brand-Saber, B. et al., "The ventralizing effect of the notochord on somite differentiation in chick embryos", <i>Anat. Embryol.</i> <u>188</u> :239-245 (1993).

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AQ	Bumcrot, D.A. and McMahon A. "Sonic Hedgehog: Making the gradient", <i>Chemistry and Biology</i> <u>3</u> (1):13-16 (Jan. 1996).
AR	Bumcrot, D.A. and McMahon, A., "Sonic signals somites", <i>Curr. Biol.</i> <u>5</u> (6):612-614 (June 1995).
AS	Bumcrot, D.A. et al., "Proteolytic Processing yields two secreted forms on sonic Hedgehog", <i>Mol. Cell. Biol.</i> <u>15</u> (4):2294-2302 (4/95).
AT	Chang et al., Products, genetic linkage and limb patterning activity of a murine hedgehog gene, <i>Development</i> 120:3339-3353, Nov. 1994.
AU	Charité, J. et al., "Ectopic Expression of <i>Hoxb-8</i> Causes Duplication of the ZPA in the Forelimb and Homeotic Transformation of Axial Structures", <i>Cell</i> <u>78</u> :589-601 (1994).
AV	Coffman et al., "Xotch, the <i>Xenopus</i> homolog of <i>Drosophila</i> notch", <i>Science</i> <u>249</u> :1438-1441 (1990)
AW	Concordet, J. and Ingham, P., "Developmental biology. Patterning goes sonic", <i>Nature</i> <u>375</u> (6529):279-280 (May 1995)
AX	Creighton, T.E., <i>Proteins Structures and Molecular Principles</i> , W.H. Freeman and Company: New York, NY, pp. 223-227.
AY	Currie et al., "Induction of a specific muscle cell type by a hedgehog-like protein in zebrafish", <i>Nature</i> <u>383</u> :452-455 (1996)
AZ	Curry et al., "Sequence analysis reveals homology between two proteins of the flagellar radial spoke", <i>Mol. Cell. Biol.</i> <u>12</u> :3967-3977 (1992)
BA	Davidson, E.H., "How embryos work: a comparative view of diverse modes of cell fate specification", <i>Devel.</i> <u>108</u> :365-389 (1990)
BB	Davis, A.P. and M.R. Capecchi, "Axial homeosis and appendicular skeleton defects in mice with a targeted disruption of <i>hoxd-1</i> ", <i>Devel.</i> <u>120</u> :2187-2198 (1994)
BC	Dickinson W., "Molecules and morphology: Where's the homology", <i>TIG</i> <u>11</u> , (4):119-120 (1995)
BD	Dingemans, M.A. et al., "The expression of liver-specific genes within rat embryonic hepatocytes in a discontinuous process", <i>Differentiation</i> <u>56</u> :153-162 (1994)
BE	Dollé, P. et al., "Coordinate expression of the murine <i>Hox-5</i> complex homoeobox-containing genes during limb pattern formation", <i>Nature</i> <u>342</u> :767-772 (1989)
BF	Dollé, P. et al., "Disruption of the <i>Hoxd-13</i> Gene Induces Localized Heterochrony Leading to Mice with Neotenic Limbs", <i>Cell</i> <u>75</u> : 431-441 (Nov. 5, 1993).

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	BX	Hammerschmidt, M. et al., "The world according to hedgehog", <i>TIG</i> <u>13</u> (1):14-21 (1997)			
	BY	Haramis, A. et al., "The limb deformity mutation disrupts the SHH/FGF-4 feedback loop and regulation of 5-HoxD genes during limb pattern formation", <i>Devel.</i> <u>121</u> (12:4161-4170 (Dec 1995)			
	BZ	Hardy, A., et al., "Gene expression, polarising activity and skeletal patterning in reaggregated hind limb mesenchyme", <i>Devel.</i> <u>121</u> (12):4329-4337 (Dec 1995)			
	CA	Hatta, K. et al., "The cyclops mutation blocks specification of the floor plate of the zebrafish central nervous system", <i>Nature</i> <u>350</u> :339-341 (1991)			
	CB	Heberlein, U. et al., "The TGBB homolog <i>dpp</i> and the segment polarity gene <i>hedgehog</i> are required for propagation of a morphogenetic wave in the <i>Drosophila</i> retina", <i>Cell</i> <u>75</u> :913-926 (1993)			
	CC	Heemskerk, J. and S. DiNardo, "Drosophila patched gene encodes a putative membrane protein required for segmental patterning", <i>Cell</i> <u>59</u> :751-765 (1989)			
	CD	Hidalgo, A. and P. Ingham, "Cell patterning in <i>Drosophila</i> segment: spatial regulation of the segment polarity gene <i>patched</i> ", <i>Devel.</i> <u>110</u> :291-301 (1990)			
	CE	Hooper, J. and Scott, M., "The <i>Drosophila</i> patched gene encodes a putative membrane protein required for segmental patterning", <i>Cell</i> <u>59</u> :751-765 (1989)			
	CF	Hynes, M., et al., "Induction of midbrain dopaminergic neurons by Sonic Hedgehog", <i>Neuron</i> <u>15</u> (1):35-44 (July 1995)			
	CG	Hynes, R.O., "Integrins: A family of Cell Surface Receptors", <i>Cell</i> <u>48</u> :549-554 (1987)			
	CH	Ingham, P.W. and A. Hidalgo, "Regulation of <i>wingless</i> transcription in the <i>Drosophila</i> embryo", <i>Devel.</i> <u>117</u> :283-291 (1993)			
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	CK	Ingham, P.W., " <i>Hedgehog</i> points the way", <i>Current Biology</i> <u>4</u> (4):347-350 (1994)			
	CL	Ingham, P.W., "Signalling by hedgehog family proteins in <i>Drosophila</i> and vertebrate development", <i>Curr. Opin. Genet. Dev.</i> <u>5</u> (4): 492-498 (Aug 1995)			
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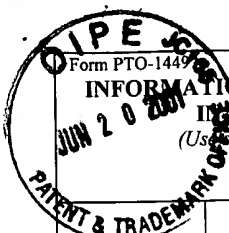
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DF	Lee, J.J. et al., "Secretion and localized transcription suggest a role in positional signaling for products of the segmentation gene <i>hedgehog</i> ", <i>Cell</i> <u>71</u> :33-50 (1992)		
DG	Lee, Se-Jin, "Expression of growth/differentiation factor 1 in the nervous system: Conservation of a bicistronic structure", <i>PNAS</i> <u>88</u> : 4250-54 (May 1991).		
DH	Lerner, R.A., Antibodies of predetermined specificity in biology and medicine, <i>Adv. Immunol.</i> , <u>36</u> : 1-44.		
DI	Levin, M. et al., "A molecular pathway determining left-right asymmetry in chick embryogenesis", <i>Cell</i> <u>82</u> (5):803-814 (Sept 1995)		
DJ	Li, W. et al., "Function of protein kinase A in hedgehog signal transduction and Drosophila imaginal disc development", <i>Cell</i> <u>80</u> (4):553-562 (Feb 1995)		
DK	Lopez-Martinez, A. et al., "Limb-patterning activity and restricted posterior localization of the amino-terminal product of Sonic hedgehog cleavage", <i>Curr Biol.</i> <u>5</u> (7):791-796 (July 1995)		
DL	Lumsden, A. and Graham, A., "Neural patterning: A forward role for hedgehog", <i>Curr Biol.</i> <u>5</u> (12):1347-1350 (Dec 1995)		
DM	Ma, C. and Moses, K., "Wingless and patched are negative regulators of the morphogenetic furrow and can affect tissue polarity in the developing Drosophila compound eye", <i>Devel.</i> <u>121</u> (8) 2279-2289 (Aug 1995)		
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DP	Marigo, V. et al., "Biochemical evidence that patched is the hedgehog receptor", <i>Nature</i> <u>384</u> 176-179 (1996)		
DQ	Marti, E. et al., "Requirement of 19K form of Sonic hedgehog for induction of distinct ventral cell types in CNS explants", <i>Nature</i> <u>375</u> : 322-325 (1995).		
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DS	Mavillo, F. et al., "Activation of four homeobox gene clusters in human embryonal carcinoma cells induced to differentiate by retinoic acid", <i>Differentiation</i> <u>37</u> :73-79 (1988)		
DT	McGinnis, W. and R. Krumlauf, "Homeobox genes and axial patterning", <i>Cell</i> <u>68</u> :283-302 (1992)		
DU	Mohler, J. and K. Vani, "Molecular organization and embryonic expression of the <i>hedgehog</i> gene involved in cell-cell communication in segmental patterning of <i>Drosophila</i> ", <i>Devel.</i> <u>115</u> :957-971 (1992)		
DV	Mohler, J., "Requirements for <i>hedgehog</i> , a segmental polarity gene, in patterning larval and adult cuticle of <i>Drosophila</i> ", <i>Genetics</i> <u>120</u> :1061-1072 (1988)		




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DW	Morgan, B.A. et al., "Targeted misexpression of <i>Hox-4.6</i> in the avian limb bud causes apparent homeotic transformations", <i>Nature</i> <u>358</u> :236-239 (1992)
DX	Munsterberg A. et al., "Combinational signaling by Sonic hedgehog and Wnt family members induces myogenic bHLH gene expression in the somite", <i>Genes Dev.</i> <u>9</u> (23):2911-2922 (Dec 1995)
DY	Nakano, Y. et al., "A protein with several possible membrane-spanning domains encoded by the <i>Drosophila</i> segment polarity gene patched", <i>Nature</i> <u>341</u> :508-513 (1989)
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EA	Niswander, L. and G.R. Martin, "FGF-4 and BMP-2 have opposite effects on limb growth", <i>Nature</i> <u>361</u> :68-71 (1993)
EB	Niswander, L. et al., "A positive feedback loop coordinates growth and patterning in the vertebrate limb", <i>Nature</i> <u>371</u> : 609-612 (Oct 1994).
EC	Nohno, T. et al., "Involvement of the <i>Chox-4</i> chicken homeobox genes in determination of anteroposterior axial polarity during limb development", <i>Cell</i> <u>64</u> :1197-1205 (1991)
ED	Nohno, T. et al., "Involvement of the Sonic hedgehog gene in chick feather formation", <i>Biochem. Biophys. Res. Comm.</i> <u>206</u> (1):33-39 (Jan 1995)
EE	O'Farrell, P.H. "Unanimity waits in the wings", <i>Nature</i> <u>368</u> :188-189 (1994)
EF	Parr, B.A. et al., "Mouse <i>Wnt</i> genes exhibit discrete domains of expression in the early embryonic CNS and limb buds", <i>Devel.</i> <u>199</u> :247-261 (1993)
EG	Patel, N.H. et al., "The role of segment polarity genes during <i>Drosophila</i> neurogenesis", <i>Genes Devel.</i> <u>3</u> :890-904 (1989)
EH	Peifer, M., "The two faces of hedgehog", <i>Science</i> <u>266</u> (5190):1492-1493 (Dec 1994)
EI	Perrimon, N., "Hedgehog and beyond", <i>Cell</i> <u>80</u> :517-520 (24 Feb. 1995)
EJ	Pham, A. et al., "The suppressor of fused gene encodes a novel PEST protein involved in <i>Drosophila</i> segment polarity establishment", <i>Genetic</i> <u>140</u> (2):587-598 (June 1995)
EK	Placzek, M. et al., "Induction of floor plate differentiation by contact-dependent, homeogenetic signals", <i>Devel.</i> <u>117</u> :205-218 (1993)
EL	Placzek, M. et al., "Orientation of commissural axons <i>in vitro</i> in response to a floor plate-derived chemoattractant", <i>Devel.</i> <u>110</u> :19-30 (1990)
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## IN AN APPLICATION

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Docket Number (Optional)

HMSU-P14-006

Application Number

09/711724

Applicant

Ingham et al.

Filing Date

23-Nov-2000

Group Art Unit

1646

EN

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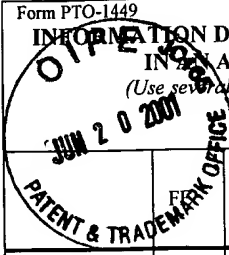
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Form PTO-1449		Docket Number (Optional) HMSU-P14-006		Application Number 09/711724	
<b>INFORMATION DISCLOSURE CITATION</b> <b>IN THIS APPLICATION</b> (Use several sheets if necessary)		Applicant Ingham et al.		Group Art Unit 1646	
		Filing Date 23-Nov-2000			
		Tabata, T. and T.B. Kornberg, "Hedgehog Is a signaling protein with a key Role in patterning Drosophila imaginal discs", <i>Cell</i> <b>75</b> :89-102 (1994)			
	FF	Tabata, T. et al., "The <i>Drosophila hedgehog</i> gene is expressed specifically in posterior compartment cells and is a target of <i>engrailed</i> regulations", <i>Genes Devel.</i> <b>6</b> :2635-2645 (1992)			
	FG	Tabin, C.J., "Retinoids, homeoboxes, and growth factors: Toward molecular models for limb development", <i>Cell</i> <b>66</b> :199-217 (1991)			
	FH	Tanabe, Y. et al., "Induction of motor neurons by Sonic hedgehog is independent of floor plate differentiation", <i>Curr. Biol.</i> <b>5</b> (6): 651-658 (June 1995)			
	FI	Tanaka E. and Gann, A., "Limb development", <i>Curr. Biol.</i> <b>5</b> (6):594-597 (June 1995)			
	FJ	Tashiro, S. et al., "Structure and expression of <i>hedgehog</i> , a <i>Drosophila</i> segment-polarity gene required for cell-cell communication", <i>Gene</i> <b>124</b> :183-189 (1993)			
	FK	Taylor, A.M. et al., "Contrasting distributions of patched and hedgehog proteins in the <i>Drosophila</i> embryo", <i>Mech. Dev.</i> <b>42</b> :89-96 (1993)			
	FL	Thaller, C. and G. Eichele, "Identification and spatial distribution of retinoids in the developing chick limb bud", <i>Nature</i> <b>327</b> :625-628 (1987)			
	FM	Tickle, C. and Eichele, G., "Vertebrate limb development", <i>Ann Rev. Cell Biol.</i> <b>10</b> :121-152 (1994)			
	FN	Tickle, C. et al., "A Quantitative Analysis of the Effect of all- <i>trans</i> -Retinoic Acid on the Pattern of Chick Wing Development", <i>Devel. Biol.</i> <b>109</b> :82-95 (1985)			
	FO	Tickle, C., "Vertebrate limb development", <i>Curr. Opin. in Gen. and Devel.</i> <b>5</b> : 478-484 (1995).			
	FP	van Straaten, H.W.M. et al., "Effect of the notochord on the differentiation of a floor plate area in the neural tube of the chick embryo," <i>Anat. Embryol.</i> <b>177</b> :317-324 (1988)			
	FQ	Vogel, A. and C. Tickle, "FGF-4 maintains polarizing activity of posterior limb bud cells in vivo and in vitro", <i>Devel.</i> <b>119</b> :199-206 (1993)			
	FR	Vortkamp et al., Regulation of rate of cartilage differentiation by Indian hedgehog and PTH-related protein, <i>Science</i> , <b>273</b> : 613-622 (2 Aug 1996).			
	FS	Wallace et al., "Oligonucleotide probes for the screening of recombinant DNA libraries", <i>Methods in Enzymology</i> <b>152</b> :432 (1987)			
	FT	Wanek, N. et al., "Conversion by retinoic acid of anterior cells into ZPA cells in the chick wing bud", <i>Nature</i> <b>350</b> :81-83 (1991)			
	FU	Wang, M. et al., "Induction of dopaminergic neuron phenotype in the midbrain by Sonic hedgehog protein", <i>Nat. Med.</i> <b>1</b> (11)-1184-1188 (Nov 1995)			

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		Wells, J., "Additivity of Mutational Effects in Proteins", <i>Biochemistry</i> 29:8509-8517 (Sept. 18, 1990).			
	FW	Yamada, T. et al., "Control of cell pattern in the developing nervous system: Polarizing activity of the floor plate and notochord", <i>Cell</i> 64:635-647 (1991)			
	FX	Yang, Y. and L. Niswander, "Interaction between the signaling molecules WNT7a and SHH during vertebrate limb development: Dorsal signals regulate anteroposterior patterning" <i>Cell</i> 80:939-947 (Mar. 1995)			
	FY	Zappavigna et al., "Hox4 genes encode transcription factors with potential auto-and cross-regulator capacities", <i>EMBO</i> 10:4177-4187 (1991)			
	FZ	Zardoya et al., "Evolution and orthology of hedgehog genes", <i>TIG</i> 12 (12):496-467 9199)			
	GA	Zecca, M. et al., "Sequential organizing activities of engrailed, hedgehog and decapentaplegic in the Drosophila wing", <i>Devel.</i> 121 (8):2265-2278 (Aug 1995)			
EXAMINER				DATE CONSIDERED	
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to the applicant.					

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